Original Article

The predictive implication of programmed cell death ligand 1 expression in extranodal natural killer/T-Cell lymphoma and its correlation with clinicopathological features: a systematic review and meta-analysis

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Background: Although programmed cell death ligand 1 (PD-L1) expression and function in hematologic malignancies have aroused extensive attention, its prognostic value for extranodal natural killer/T-cell lymphoma (ENKTL) is still unknown. Therefore, we conducted this meta-analysis to explore the predictive value of neoplastic PD-L1 expression for ENKTL.

Methods: The PubMed, Embase, Web of Science, and CNKI databases were searched to identify eligible observational studies reporting PD-L1 expression and survival outcomes of ENKTL patients. The search was conducted in accordance with the Meta-analyses Of Observative Studies in Epidemiology (MOOSE) guidelines. The pooled hazard ratios (HRs) and 95% confidence intervals (95% CIs) were adopted to analyze survival outcomes, and the odds ratios (ORs) and 95% CIs were adopted for clinicopathological parameters. Review Manager 5.3 and STATA 17.0 were used for statistical analysis. Potential publication bias was evaluated by funnel plot and Egger's test.

Results: A total of 433 patients with ENKTL were included across seven studies. The pooled results showed no significant relationship between neoplastic PD-L1 expression and overall survival (OS) (HR =1.35, 95% CI: 0.49–3.75, P=0.559). We also performed subgroup analyses. However, increased PD-L1 expression was associated with a low international prognostic index (IPI) score of 0–1 (OR =2.46; 95% CI: 1.11–5.45, P=0.03), good performance status (OR =1.97; 95% CI: 1.11–3.51, P=0.02), and a good treatment effect (OR =2.61; 95% CI: 1.01–6.70, P=0.05).

Conclusions: PD-L1-positive expression in patients with ENKTL was correlated with favorable clinical features. Thus, PD-L1-positive expression appears to be a potential predictor of treatment benefits. Additional large-scale, high-quality studies are needed to further explore its predictive value.

Keywords: Extranodal natural killer/T-cell lymphoma (ENKTL); programmed cell death ligand 1 (PD-L1); prognosis; therapy; meta-analysis

Submitted Dec 17, 2022. Accepted for publication Jul 14, 2023. Published online Aug 28, 2023.
doi: 10.21037/tcr-22-2569
View this article at: https://dx.doi.org/10.21037/tcr-22-2569

Introduction

Extranodal natural killer/T-cell lymphoma (ENKTL) is a highly aggressive malignant lymphoma with a cytotoxic phenotype, that is relatively frequent in Southeast Asia including China, but rare in Western countries (1). In China, ENKTL accounts for approximately 5–16% of all types of lymphomas (1). It is closely associated with the Epstein-Barr virus infection which the nose is the typical initial site, and is histologically characterized by tissue necrosis and vascular destruction. In particular, patients often present heterogeneous clinical characteristics and prognoses (2). Despite the emergence of new chemotherapy or targeted therapies, the prognosis of ENKTL is still poor, especially in relapsed or refractory patients (3). Therefore, it is vital to identify novel predictive biomarkers and potential therapeutic targets for ENKTL.

At present, the programmed cell death ligand 1/programmed cell death receptor 1 (PD-L1/PD-1) pathway has been identified as a critical factor in tumor immune evasion in many solid tumors (4) and lymphoid malignancies, including Hodgkin lymphoma (5,6). Recent studies have revealed PD-L1 as a new prognostic factor for survival in ENKTL (7). In addition, monoclonal antibody blockade of the PD-L1/PD-1 pathway has been performed gradually and partially achieved the treatment effect in ENKTL (3). However, the prognostic role of PD-L1 expression in ENKTL remains unclear. Kim *et al.* (8) have shown that PD-L1 positivity on tumor cells was related to a better prognosis. In contrast, other researchers have reported inconsistent results (9,10).

To address the above question, we conducted a meta-analysis to assess the predictive implication of neoplastic PD-L1 expression and the relationship between PD-L1 expression and clinicopathological parameters in ENKTL. This meta-analysis was carried out in accordance with the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) reporting checklist (11) (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2569/rc).

Highlight box

Key findings

- The pooled results did not find a correlation between PD-L1 expression and overall survival in patients with ENKTL, but indicated that PD-L1 positive expression was a fa-vorable factor associated with the better clinical features. It appears to be a potential in-dicator for predicting the treatment benefits.

What is known and what is new?

- As a highly aggressive neoplasm, ENKTL presented a poor prognosis. The rise of PD-1/PD-L1 blockade in recent years provided a promising treatment strategy to some tumors. However, it is still unclear about the relationship between PD-L1 expression and ENKTL.
- We conducted a meta-analysis to assess the predictive implication of neoplastic PD-L1 expression and the relationship between PD-L1 expression and clinicopathological parameters in ENKTL.

What is the implication, and what should change now?

- We have found PD-L1 positive expression in patients with ENKTL was correlated with favorable clinical features. Based on these findings, patients who may benefit from therapy can be screened. Considering our limitations and many immunotherapeutic schemes still under exploration, further high-quality studies on a larger scale are required for exploring its predictive value.

Methods

Search strategy

The research question was defined based on the PICO principles from the PRISMA statement: 'P' (population) refers to the patients with a definite diagnosis of extranodal NK/T-cell lymphoma; 'I' (intervention) refers to the assessment of neoplastic PD-L1 expression on tissues via immunohistochemistry (IHC); 'C' (comparison) refers to the comparison between positive and negative PD-L1 expression; and 'O' (outcomes) refers to the survival outcomes and clinicopathological features.

We searched the PubMed, Embase, Web of Science, and CNKI electronic databases up to March 2022 without restrictions on language or region. Free-text and Medical Subject Heading (MeSH) searches were employed for keywords. The main search terms were as follows: 'Lymphoma, Non-Hodgkin'[Mesh] OR 'Lymphoma, T-Cell'[Mesh] OR 'Lymphoma, Extranodal NK-T-Cell'[Mesh] AND (B7-H1 OR PD-L1 OR CD274 OR 'Programmed cell death ligand 1'). Furthermore, we carefully checked the references of each relevant article to prevent omissions of related literature that satisfied the eligibility criteria.

Inclusion and exclusion criteria

Potential articles were evaluated by two reviewers independently. The inclusion criteria were as follows: (I) ENKTL was histologically diagnosed according to the

WHO classification for lymphomas; (II) PD-L1 expression on tumor cells was detected on tissue sections by IHC staining; (III) the relationship of PD-L1 expression with prognosis and clinicopathological features, containing patient cases separately; and (IV) the hazard ratio (HR) and 95% confidence interval (95% CI) were directly provided or could be calculated from the available data. The exclusion criteria were as follows: (I) all articles published as a review, letter, case report, comment, or animal study; (II) the data for estimating the HR and 95% CI were insufficient; (III) the cutoff value of PD-L1 positive expression was not reported; (IV) targets were restricted to nonmalignant cells or soluble PD-L1 expression in ENKTL patients; (V) the latest or most complete sample was collected when the same patient population appeared in different studies.

Data extraction

Two investigators independently extracted the relevant data from each article, and any issues were resolved by discussion or by consulting a third investigator. The following data were extracted: first author, publication year, country of origin, the total number of patients, stage, median follow-up time, evaluation method, antibody information, cutoff value of PD-L1 positivity on tumor cells, PD-L1-positive expression rate, number of patients with positive or negative cases, clinicopathological parameters, HRs and 95% CIs for OS, progression-free survival (PFS) or event-free survival (EFS). We extracted the HRs and 95% CIs preferentially from multivariable analyses. Then the HR and 95%CI were retrieved from Kaplan-Meier curves via Engauge-Digitizer 4.1 software (http://markummitchell.github.io/engauge-digitizer) if they were not reported directly in studies (12).

Quality assessment

The quality of all included retrospective studies was assessed by two investigators using the Newcastle-Ottawa scale (NOS) (13). The maximum score was 9, and studies with scores of 6 or above were considered high quality. Disagreements were resolved through discussion.

Statistical analysis

Our primary endpoint was OS. The secondary endpoints were PFS or EFS. The adjusted HR and 95% CI were adopted as effect sizes (ESs) to assess the impact of PD-L1-positive expression on cumulative survival outcomes. In addition, the correlation between PD-L1 expression and clinicopathological features was evaluated using the odds ratio (OR) and 95% CI.

Two software programs were used to analyze all statistics: Review Manager 5.3 (Revman, the Cochrane Collaboration; Oxford, UK) and STATA version 17.0 (Stata Corporation; College Station, TX, USA). Heterogeneity was assessed with a chi-squared test and I^2 statistics. A fixed effects model was applied when $P>0.05$ or $I^2<50\%$, indicating no significant heterogeneity among studies; otherwise, a random-effects model was selected. The sources of heterogeneity were explored through subgroup analysis. Potential publication bias was evaluated by funnel plot and Egger's test. Sensitivity analysis was used to assess the stability of the final results. In addition, we tried to identify the sources of heterogeneity through subgroup analysis. $P<0.05$ indicated statistical significance.

Results

Literature retrieval and study characteristics

A total of 607 studies were obtained by searching the four above databases. Based on the inclusion and exclusion criteria, 335 articles were removed after screening the titles and abstracts due to being irrelevant, being a review, being a comment, or a lack of comparative data. Thirty-five studies underwent further full-text review. Among them, 2 articles (14,15) on overlapping cases from the same institution and one article (16) on PD-L1 evaluation covering nonneoplastic immune cells were removed. Ultimately, 7 eligible articles were collected for the meta-analysis. The flowchart of the study secletion process is presented in *Figure 1*.

Seven studies encompassing 433 patients from Asia (2 in Korea, 1 in Thailand, and 4 in China) were included. All studies were retrospective (8-10,17-20). The studies were published from 2014 to 2021. Two articles published in Chinese were retrieved from PubMed (18,20). Among the 7 included articles, 6 studies (8-10,17,19,20) analyzed OS and PD-L1 expression, and 2 studies (10,17) reported PFS and EFS. IHC staining was performed in all studies to measure PD-L1 expression on tumor cells. The cutoff value to define PD-L1 positivity was determined using the form of percentage or semiquantitative analyses but was not precisely consistent within the articles. The main characteristics are summarized in *Table 1*.

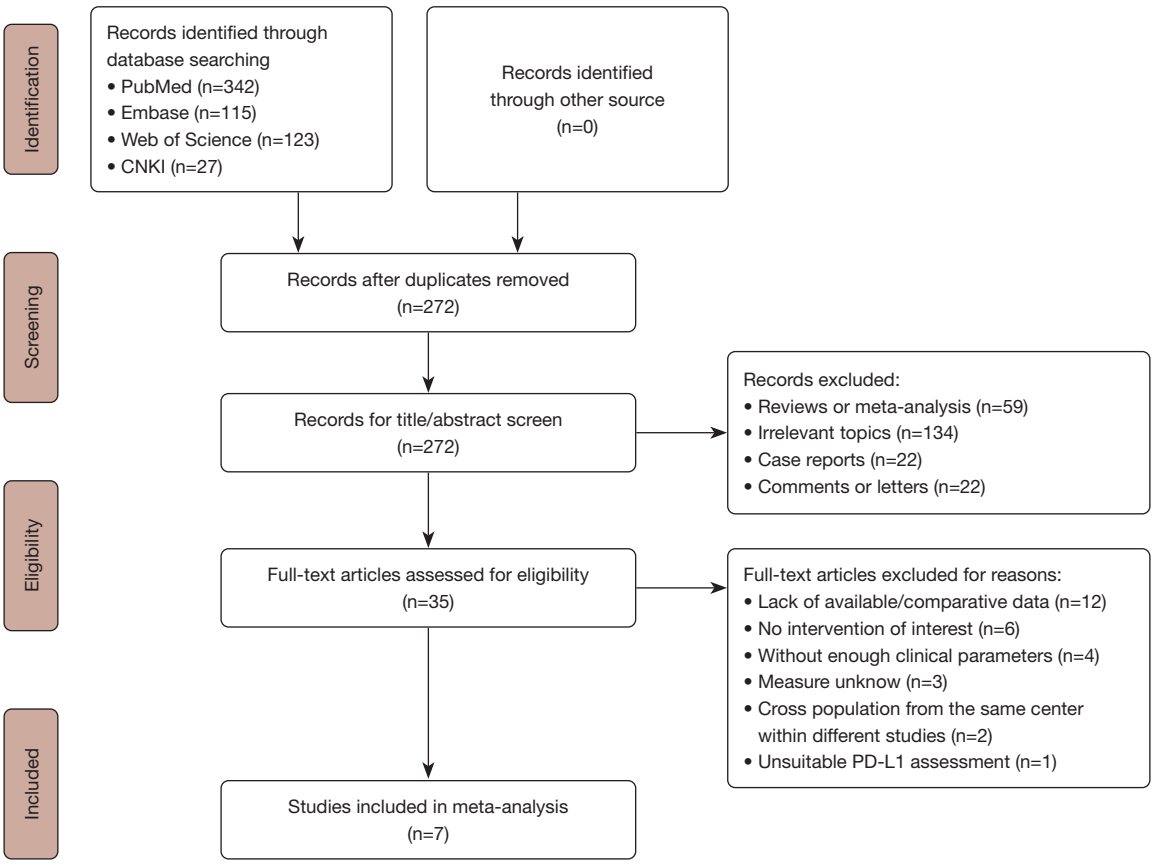

Figure 1 The inclusion flowchart of study retrieval. PD-L1, programmed cell death ligand 1.

Prognostic significance of PD-L1 expression in ENKTL

Association between PD-L1 expression and OS and PFS/EFS

There were 403 cases from 6 studies investigating the relationship between PD-L1 expression and OS in ENKTL (8-10,17,19,20). The HRs and 95% CIs were provided directly in four studies (8,10,17,19) and retrieved from survival curves in another two articles (9,20). The pooled HR indicated that PD-L1 expression was not associated with OS in patients with ENKTL (HR =1.35, 95% CI: 0.49–3.75, P=0.559) (*Figure 2A*).

Only 2 out of 7 articles, including 158 patients, examined PFS/EFS analyses (10,17). A random-effects model was employed due to heterogeneity within the studies (P=0.082, I^2=67%). The pooled analyses revealed that PD-L1 overexpression was not related to PFS in ENKTL patients (HR =3.11, 95% CI: 0.42–22.92, P=0.266) (*Figure 2B*).

Subgroup analysis of OS and sensitivity analysis

We tried to identify the sources of heterogeneity through subgroup analysis. The analyses were stratified by location, the cutoff value of PD-L1 positivity, and the PD-L1 antibody company (*Table 2*).

The subgroup analysis suggested that PD-L1 expression was not related to OS in patients with ENKTL either from China or other Asian countries. The subgroup analysis based on cutoff value demonstrated that patients with high PD-L1 expression had a favorable predictive value when a cutoff value of 10% was used (HR =0.38, 95% CI: 0.18–0.78, P=0.009; I^2=0%, P=0.877), but there was no correlation when using 5% as the threshold (HR =4.05, 95% CI: 0.36–45.39, P=0.256; I^2=87.6%, P=0.000). For the PD-L1 antibody company, the pooled results showed that an effect of elevated PD-L1 expression on OS was not observed whether the PD-L1 antibody came from Cell Signaling Technology (CST).

Table 1 The main characteristics of the studies included in the meta-analysis

First author	Year	Country	Sample size	Median age (year)	Ann arbor stage	Outcome	HR source	Prognostic value	Median follow-up (month)	Therapy	Quality assessment (NOS)	PD-L1 positive	Cut-off value	Antibody company	Antibody clone	Dilution
Kim (8)	2016	Korea	73	8–79*	I–IV	OS	HR	Good	20.6	CT/RT/CRT/S	7	56.2% (41/73)	10%	Cell Signaling, USA	E1L3N	NA
Jo (9)	2017	Korea	79	NA	I–IV	OS	K-M	NR	52.4	CT/RT/CRT/CCRT	7	79.7% (63/79)	5%	R&D Systems, USA	NA	1:200
He (10)	2021	China	109	41	I–IV	OS, PFS	HR	Poor	NA	CT	6	41.3% (45/109)	32.5%	Cell Signaling, USA	E1L3N	NA
Muhamad (17)	2020	Thailand	49	51	I–IV	OS, EFS	HR	Poor	18	CT/RT/CRT	7	61.2% (30/49)	5%	Cell Signaling, USA	E1L3N	1:400
Han (18)	2014	China	30	47	I–IV	NA	NA	NA	NA	NA	6	60% (18/30)	3 score	Proteintech, USA	NA	1:120
Zeng (19)	2019	China	42	41	I–II	OS	HR	Poor	60.1	CT/RT/CCRT	6	59.5% (25/42)	5%	ZSGB-BIO	SP142	NA
Zhang (20)	2020	China	51	48	I–IV	OS	K-M	Good	19	NA	7	76.5% (39/51)	10%	Dako	22C3	1:100

*, age range was presented. HR, hazard ratio; NOS, Newcastle-Ottawa Scale; PD-L1, programmed cell death ligand 1; OS, overall survival; CT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy; CCRT, concurrent chemoradiotherapy; S, surgery; K-M, Kaplan-Meier curve; NR, not relevant; NA, not available; PFS, progression-free survival; EFS, event-free survival.

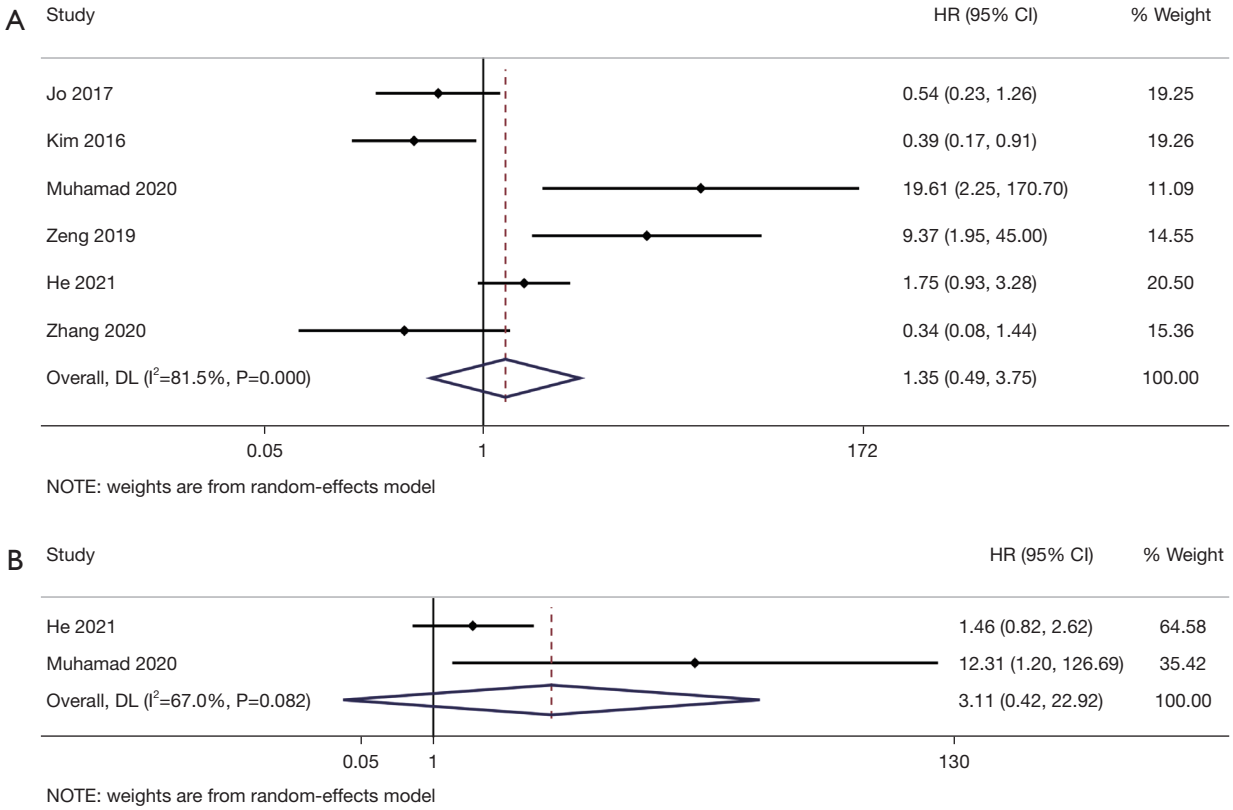

Figure 2 Forest plots illustrating the association between PD-L1 expression and survival outcomes in ENKTL. (A) OS; (B) PFS/EFS. HR, hazard ratio; CI, confidence interval; PD-L1, programmed cell death ligand 1; ENKTL, extranodal natural killer/T-cell lymphoma; OS, overall survival; PFS, progression-free survival; EFS, event-free survival.

Table 2 Subgroup analysis for OS with positive PD-L1 expression

Stratified analysis	No. of studies	No. of patients	Pooled HR (95% CI)	P value	Heterogeneity		
					I^2 (%)	P value	Model
Location							
China	3	202	1.73 (0.39–7.66)	0.472	78.5	0.009	Random
Non-China	3	201	1.10 (0.24–5.06)	0.906	81.9	0.004	Random
Cut-off value							
5%	3	170	4.05 (0.36–45.39)	0.256	87.6	0.000	Random
10%	2	124	0.38 (0.18–0.78)	0.009	0.0	0.877	Fixed
32.5%	1	109	1.75 (0.93–3.29)	0.082	–	–	–
PD-L1 antibody company							
CST	3	231	1.76 (0.36–8.55)	0.485	86.3	0.001	Random
Non-CST	3	172	1.12 (0.19–6.57)	0.898	82.8	0.003	Random

OS, overall survival; PD-L1, programmed cell death ligand 1; HR, hazard ratio; CI, confidence interval; CST, Cell Signaling Technology.

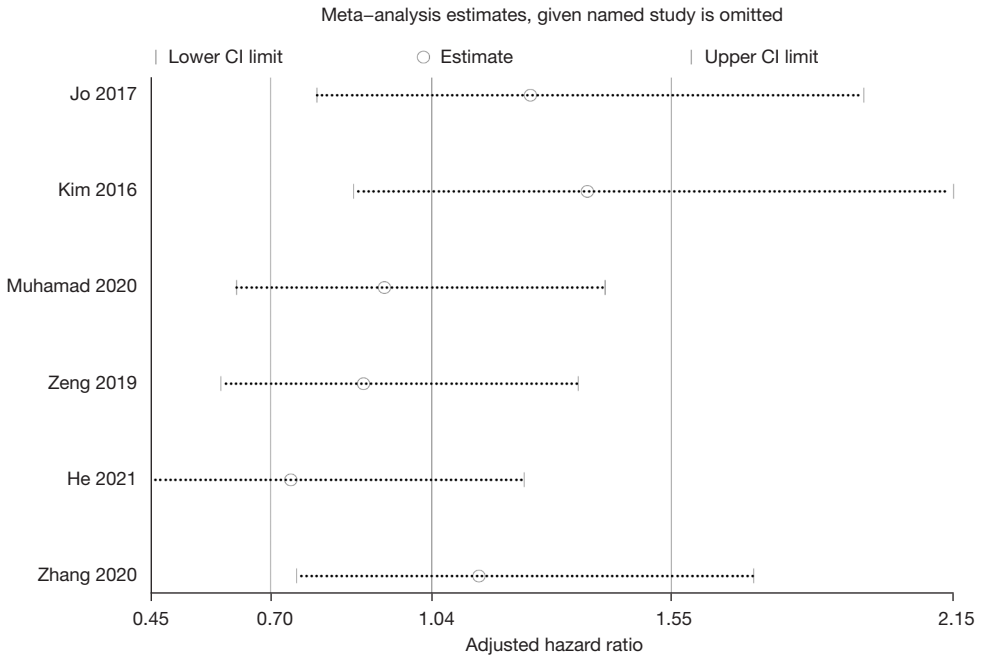

Figure 3 Sensitivity analysis for the meta-analysis among those studies reporting OS. CI, confidence interval; OS, overall survival.

Meta-analysis was applied with a random effects model due to strong heterogeneity among the studies (P=0.000, I^2=81.5%) (*Figure 2A*). Sensitivity analysis showed that the adjusted HRs were not significantly influenced by any single study, thus suggesting that the results were reliable (*Figure 3*).

Correlation of PD-L1 expression with clinicopathological features

We also conducted meta-analyses to explore the relationship of increased PD-L1 expression with various clinicopathological characteristics. Statistical associations of PD-L1 positivity were shown with slight performance status, low international prognostic index (IPI) score, and better treatment effect tendency (*Figure 4*). Nevertheless, the associations were not significant between PD-L1 expression and age, sex, B symptoms, Ann Arbor stage, primary sites, prognostic index of natural killer lymphoma (PINK) model, lymph node invasion, or lactic dehydrogenase (LDH) level (*Table 3*).

Eastern Cooperative Oncology Group (ECOG) score

Five studies comprising 337 patients evaluated the relationship of PD-L1 expression with ECOG scores (8-10,17,18). Among 249 patients with ECOG scores from 0–1, 147 (59%) were positive for PD-L1 expression, and 50 (56.8%) of 88 patients with ECOG score ≥2 were PD-L1 positive. The fixed effects model was used due to the lack of heterogeneity among studies (P=0.94, I^2=0%). The pooled analysis indicated that increased PD-L1 expression was correlated with better performance status (OR =1.97; 95% CI: 1.11–3.51, P=0.02) (*Figure 4A*).

IPI score

The association between PD-L1 expression and IPI score was examined in two studies containing 137 patients (8,9). There rates of PD-L1 overexpression were 80.3% (53/66) and 62% (44/71) in patients with IPI scores of 0–1 and ≥2, respectively. The fixed effects model was applied (P=0.29, I^2=10%). The results indicated that high PD-L1 expression was more common in ENKTL patients with IPI scores of 0–1 (OR =2.46; 95% CI: 1.11–5.45, P=0.03) (*Figure 4B*).

Therapeutic outcome

Two studies, including 81 patients, were combined to analyze the relationship between PD-L1 expression and the objective response rate (ORR) (8,18). Of the 52 patients with complete response (CR) or partial response (PR), 37 (71.2%) were PD-L1 positive, while 14 (48.3%) out of

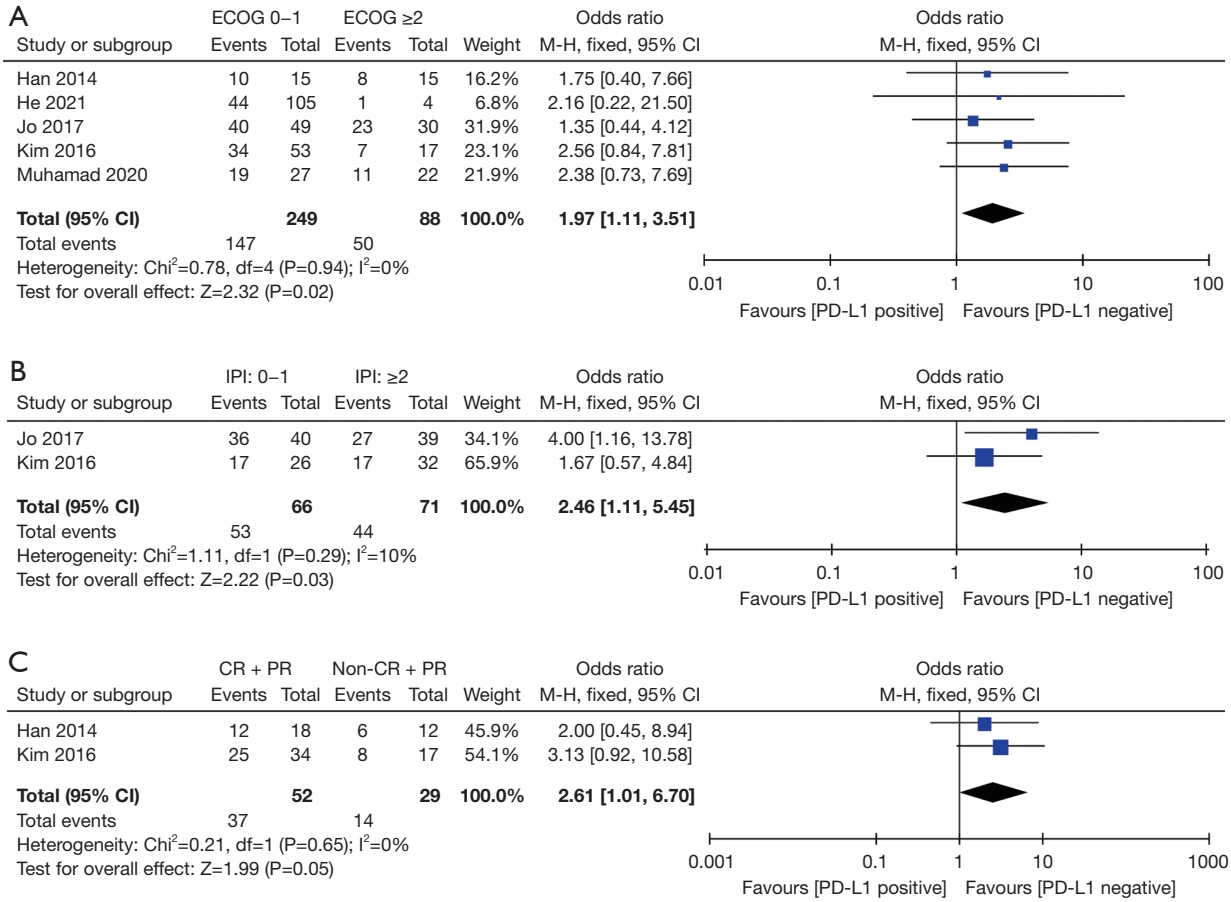

Figure 4 Forest plots illustrating the association between PD-L1 expression and clinicopathological features in ENKTL. (A) ECOG; (B) IPI score; (C) therapeutic outcome. ECOG, Eastern Cooperative Oncology Group; M-H, Mantel-Haenszel; CI, confidence interval; PD-L1, programmed cell death ligand 1; IPI, international prognostic index; CR, complete response; PR, partial response.

Table 3 Association between PD-L1 expression and other clinicopathological features

Clinicopathological parameters	No. of studies	No. of patients	Model	Pooled OR	95% CI	P value	Heterogeneity	
							I^2 (%)	P value
Age, <60 *vs.* ≥60 years	5	340	Fixed	1.44	0.84–2.46	0.18	0	0.83
Gender, male *vs.* female	3	188	Fixed	1.16	0.62–2.15	0.64	20	0.28
B symptom, yes *vs.* no	3	229	Random	1.16	0.42–3.14	0.78	62	0.07
Stage, I–II *vs.* III–IV	5	335	Random	0.64	0.31–1.32	0.23	51	0.09
Lymph node invasion, none/regional *vs.* distant	3	237	Fixed	1.82	0.92–3.59	0.08	25	0.26
PINK, 0–1 *vs.* 2–4	3	236	Random	0.76	0.23–2.52	0.65	71	0.03
Primary site, UAT *vs.* Not-UAT	2	180	Random	1.12	0.35–3.56	0.85	65	0.09
LDH level, elevated *vs.* normal	4	298	Random	0.62	0.25–1.54	0.30	61	0.05

PD-L1, programmed cell death ligand 1; OR, odds ratio; CI, confidence interval; PINK, prognostic index of natural killer lymphoma; UAT, upper aerodigestive tract; LDH, lactic dehydrogenase.

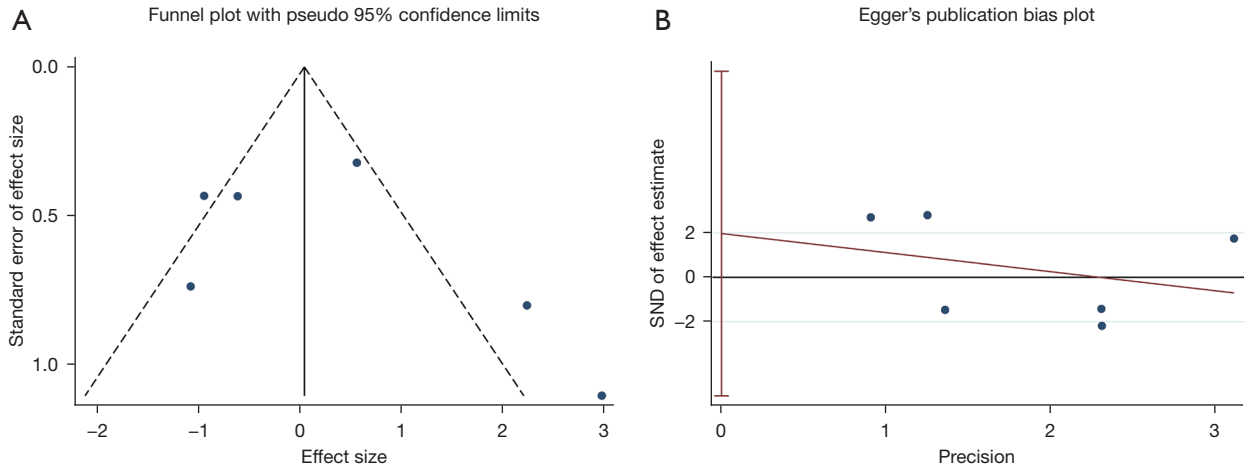

Figure 5 Plots for potential publication bias among those studies reporting OS. (A) Funnel plot; (B) Egger's test. SND, standard normal distribution; OS, overall survival.

29 patients without remission were PD-L1 positive. We used the fixed effects model due to the lack of significant heterogeneity (P=0.65, I^2=0%). The pooled analysis revealed that PD-L1-positive patients showed a trend toward a better response to therapy (OR =2.61; 95% CI: 1.01–6.70, P=0.05) (*Figure 4C*).

Publication bias

We constructed a funnel plot for survival outcome to assess symmetry via Stata17.0 software. The funnel plot was symmetrical, suggesting no or slight publication bias for OS (*Figure 5A*). Although publication bias analysis is not recommended when fewer than ten articles are included (21), Egger's test (P=0.496) was utilized to thoroughly examine publication bias. No evident asymmetry among these studies was displayed (*Figure 5B*).

Discussion

Over the past few years, studies on immune checkpoints focusing on PD-1/PD-L1 have received widespread attention. This hotspot pathway plays an essential role in promoting tumor immune escape, and PD-L1 overexpression is associated with clinical prognosis and therapeutic effects in solid tumors (22-24). Some reports have shown that increased PD-L1 expression is regarded as an inferior prognostic factor for lymphomas, such as diffuse large B-cell lymphoma (DLBCL) and Hodgkin's disease (25,26). As a highly aggressive neoplasm, ENKTL presents a poor prognosis. The rise of PD-1/PD-L1 blockade in recent years has provided a promising treatment strategy. Additionally, the positive rate of PD-L1 expression on lymphoma cells in ENKTL ranged from 39% to 100% among different studies (27,28). However, it remains unclear whether increasing PD-L1 expression in ENKTL affects survival outcomes or other clinical parameters. Related studies have observed inconsistent results on the issue (8,17). Moreover, the low incidence rate and geographical distribution of ENKTL have resulted in a lack of prospective studies on a large scale. Therefore, a meta-analysis is vital to evaluate and reach more definitive results.

According to prior inspection, the present meta-analysis is the first systematic exploration of the predictive value of neoplastic PD-L1 expression in ENKTL. We included seven eligible studies (8-10,17-20). The pooled HR of 403 patients from six articles indicated no association between neoplastic PD-L1 expression and OS. This result was in agreement with that of Zhao (28), who demonstrated that PD-L1-positive expression was a poor predictor of DLBCL but not in ENKTL (29). Similarly, no significant correlation of PFS/EFS was obtained. The possible explanation for this result might be as follows: on the one hand, the small number of sample sizes involved because of limited incidence of ENKTL; on the other hand, the follow-up time in several cohorts we included was not long enough. Moreover, strong heterogeneity was present within the studies. Although IHC was performed to detect PD-L1 expression in all studies, various antibody clones, procedures, and thresholds were adopted in different studies.

All patients from the enrolled studies were from Asia, which was consistent with the racial and geographical predisposition of ENKTL. It is essential to collect relevant studies as comprehensively as possible and include high-quality papers in languages other than English, given that ENKTL is a rare disease that tends to be frequent in Southeast Asian countries, especially in China. Additionally, it is helpful to reduce publication bias. Eventually, we performed Egger's test which is a quantitative assessment of publication bias; the results indicated that there was no significant publication bias. All the included articles were considered to be high-quality according to the NOS.

In addition to bias, heterogeneity is inevitable. Subgroup analysis did not show that the predictive value of PD-L1 differed between China and other Asian locations. However, PD-L1 was a beneficial factor for OS when the cutoff value was equal to or greater than 10%. Unfortunately, only two included studies used this cutoff value. Moreover, He *et al.* (10) obtained a 32.5% threshold for PD-L1 overexpression based on analyzing the receiver operating characteristic (ROC) curve, which was distinct from those of other articles enrolled. This difference in the cutoff value of PD-L1 might be one of the main reasons for the discordant results and heterogeneity. There is no uniform threshold for neoplastic PD-L1 expression in non-Hodgkin's lymphoma (NHL). Additionally, increased prognostic significance was demonstrated in DLBCL when the cutoff value was ≥30% (30). In addition, Bi *et al.* (14) reported that a cutoff value >38% was an independent adverse prognostic factor for OS and PFS in ENKTL, which might be related to NF-κB pathway activation. Hence, standardizing high/low PD-L1 expression determination criteria is necessary for future PD-L1 detection and research comparability. IHC has become a common method for the diagnosis and treatment of many diseases. Additionally, the challenges vary among different diseases, including the temporal and spatial heterogeneity of tissue expression, the setting of grading and quantitative assessment criteria, the threshold of positive expression, etc. For rare diseases, immunostaining standardization is more challenging due to the lack of large-scale study verification and unconsolidated interpretation methods. As a milestone in the era of immunotherapy, PD-L1 can not only serve as a prognostic indicator but also guide the clinical application of PD-L1/PD-1 inhibitors and may predict the efficacy of treatment. Therefore, the IHC staining and interpretation of this biomarker should be strictly treated. Due to the lack of sufficient data, the PD-L1 expression of ENKTL cannot have a uniform threshold like other solid tumors. This would cause some confusion in clinical medication and prognosis monitoring, which is also an issue that needs to be focused on and solved in the future.

Our analysis also revealed that ENKTL patients with PD-L1 positivity presented lower IPI scores, milder performance status, and higher ORR than PD-L1-negative patients. Increased PD-L1 expression has been shown to be associated with favorable clinical manifestations. This result was similar to that of Jo *et al.* (9), who demonstrated that PD-L1 positivity was linked to normal LDH levels and lower IPI scores. Furthermore, more studies are needed to explore the mechanism of favorable indicators of PD-L1 positivity in ENKTL.

High expression of PD-L1 was good for patients to benefit from targeted immunotherapy or chemotherapy treatment, suggesting that PD-L1 would be a potential predictor for the treatment benefits (16). In our two analyzed articles, patients were treated with radiotherapy, chemotherapy, or both (8,18). Although the pooled P value was at the threshold (P=0.05), it presented a good response tendency. Several clinical trials on PD-1/PD-L1 inhibitors were mainly performed on patients with relapsed or refractory ENKTL who previously failed to respond to chemotherapies, with an ORR of 43–100% (31-33). In addition, patients with high PD-L1 expression were often more likely to experience remission than those with negative expression (20,31). Furthermore, Cai *et al.* (34) reported that 5/6 patients with PD-L1 overexpression obtained and maintained CR with the anti-PD-1 antibody plus P-GEMOX regimen in advanced NK/T-cell lymphoma. The possible mechanisms include local depletion of cytokines involved in cancer cell survival and growth (8), STAT3/JAK3/PD-L1 alterations, and ARID1A mutation. However, the lack of a control group is a limitation of this study.

Notably, it has been reported that PD-L1 positivity could induce chemoresistance in breast cancer and DLBCL (35,36). However, a trend of superior clinical response was presented in ENKTL patients receiving chemotherapy with PD-L1 positivity in our meta-analysis. Interestingly, enhanced PD-L1 expression may improve the effects of chemotherapy in patients with melanoma and colon carcinoma (37,38). Thus, the function of PD-L1 in chemoresistance probably depends on disease context or cancer type (39). In addition, Horibe *et al.* (40) found constant upregulation of PD-L1 expression during chemotherapy in urothelial carcinoma. Moreover, good therapeutic effects were approved for maintenance therapy

with anti-PD-1 inhibitors. Therefore, did similar changes exist for some advanced or refractory patients with a poor response to prior chemotherapy but a significant response to PD-1/PD-L1 blockade? Therefore, further prospective clinical trials are required to explore and clarify the need for combined checkpoint targeted treatment in ENKTL at initial therapy.

Despite our best efforts, this meta-analysis does have limitations. First, the number of patients enrolled in these studies was relatively limited because of the rarity of ENKTL worldwide. The follow-up time in certain cohorts was not long enough. Thus, studies with larger sample sizes are required to comprehensively evaluate the correlation between PD-L1 positivity and survival outcomes. Second, significant heterogeneity existed among different studies. The subgroup analysis suggested that the threshold might affect the results. There was no precise definition for the most appropriate cutoff value for stratification in ENKTL. Moreover, various PD-L1 antibodies and interpretation criteria were applied. Therefore, it is necessary to establish a uniform standard in these aspects. Third, several different treatment regimens were used within studies and could affect the prognostic role of PD-L1 expression. After high-quality re-evaluation in future studies, more reliable evidence could be provided to predict prognosis.

Conclusions

Our meta-analysis is the first study to report the predictive value of neoplastic PD-L1 expression in ENKTL. The results support that PD-L1-positive expression is a favorable factor associated with lower IPI scores, better performance status, and a tendency toward good treatment outcomes. Based on these findings, patients who may benefit from therapy can be screened. Considering our limitations and the many immunotherapeutic schemes still under exploration, further multicenter, larger-scale studies are needed to evaluate the prognostic value of PD-L1 in different treatment regimens.

Acknowledgments

We would like to thank Dr. Xiaojie Wang (Department of Colorectal Surgery, Fujian Medical University Union Hospital) for generously sharing his experience.

Funding: This work was supported by the Startup Fund for Scientific Research, Fujian Medical University (No. 2018QH1045 to W Li), and The Fourth Batch of Hospital Key Discipline Construction Projects of Fujian Medical University Union Hospital (No. 0216002# to Y Yang). The funding sources had no role in the study design, data collection, data analysis, data interpretation, writing of the report or in the decision to submit for publication.

Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2569/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2569/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2569/coif). WL received funding support from Startup Fund for Scientific Research, Fujian Medical University (No. 2018QH1045). YY received support on article processing charges from The Fourth batch of Hospital Key Discipline Construction Projects of Fujian Medical University Union Hospital (No. 0216002#). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Li W, Zheng Q, Luo X, Zhang X, Zheng X, Yang Y. The predictive implication of programmed cell death ligand 1 expression in extranodal natural killer/T-Cell lymphoma and its correlation with clinicopathological features: a systematic review and meta-analysis. Transl Cancer Res 2023;12(8):2115-2127. doi: 10.21037/tcr-22-2569

